OHDSI Large-Scale Evidence Generation and Evaluation in a Network of Databases

**Version:** 0.1

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# List of abbreviations

CYCLOPS Cyclic coordinate descent for logistic, Poisson and survival analysis

ECT Electroconvulsive therapy

MedDRA Medical Dictionary for Regulatory Activities

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

PS Propensity Score

SARI Serotonin antagonist and reuptake inhibitor

SNRI Serotonin–norepinephrine reuptake inhibitor

SSRI Selective serotonin reuptake inhibitor

TCA Tricyclic antidepressant

# Abstract

To do

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Date | Author(s) | Comments |
|  |  |  |  |

# Milestones

|  |  |
| --- | --- |
| Milestone | Planned / Estimated Date |
| Start of analysis |  |
| End of analysis |  |
| Posting of results |  |
| Submission of manuscript |  |

# Rationale and Background

To do

# Research Questions and Objectives

## Research Questions

In this study, we are interested in every pairwise comparison between any two treatments in table 1.

|  |  |  |
| --- | --- | --- |
| **Type** | **Class** | **Treatment** |
| Drug | Atypical | Bupropion |
| Drug | Atypical | Mirtazapine |
| Procedure | ECT | Electroconvulsive therapy |
| Procedure | Psychotherapy | Psychotherapy |
| Drug | SARI | Trazodone |
| Drug | SNRI | Desvenlafaxine |
| Drug | SNRI | duloxetine |
| Drug | SNRI | venlafaxine |
| Drug | SSRI | Citalopram |
| Drug | SSRI | Escitalopram |
| Drug | SSRI | Fluoxetine |
| Drug | SSRI | Paroxetine |
| Drug | SSRI | Sertraline |
| Drug | SSRI | vilazodone |
| Drug | TCA | Amitriptyline |
| Drug | TCA | Doxepin |
| Drug | TCA | Nortriptyline |

**Table 1**. List of depression treatments considered in this study

For each comparison of two treatments, we are interested in the comparative effect on each of the outcomes listed in table 2.

|  |  |
| --- | --- |
| Acute liver injury | Hypotension |
| Acute myocardial infarction | Hypothyroidism |
| Alopecia | Insomnia |
| Constipation | Nausea |
| Decreased libido | Open-angle glaucoma |
| Delirium | Seizure |
| Diarrhea | Stroke |
| Fracture | Suicide and suicidal ideation |
| Gastrointestinal hemorrhage | Tinnitus |
| Hyperprolactinemia | Ventricular arrhythmia and sudden cardiac death |
| Hyponatremia | Vertigo |

**Table 2.** Outcomes of interest considered in this study

Primary research question

* For each comparison between two depression treatments, for each of the outcomes of interest, what is the hazard ratio?

## Objectives

Primary objective

* Generate evidence for the comparative effectiveness for each pairwise comparison of depression treatments for the outcomes of interest.

Secondary objectives

* Show the feasibility of performing such an analysis at scale.
* Asses the bias inherent in each analysis by including negative and positive control outcomes.

# Research methods

## Study Design

### Overview

This study will be a set of retrospective, observational, new-user cohort studies. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘new-user’ we mean we will only analyze the first exposure of a subject to the treatment of interest. By ‘cohort study’ we mean two cohorts, a tareget and comparator cohort, will be followed from index date (start of first exposure) to some end date, and assessed for the occurrence of the outcomes of interest.

The target cohort will be new users of any of the treatments listed in table 1. The comparator cohort will be new users of another treatment listed in table 1. For both groups we restrict to people with a prior diagnosis of depression, and no prior history of bipolar disorder or schizophrenia. Each comparison is restricted to the calendar time when both treatments are observed in the data. The outcomes of interest are listed in table 2.Proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts. The time at risk starts at the day of initiation of treatment, and ends at the end of treatment or end of observation. Multiple prescriptions or therapies are considered a single exposure era using a maximum allowed gap of 30 days between treatments.

Adjustment for baseline confounders will be done by fitting a propensity model and creating propensity scores (PS). These PS will be used to stratify the target and comparator cohorts, and the proportional hazards outcome models will be conditioned on the strata.

Negative control outcomes (outcomes not believed to be caused by any depression treatment) will also be included. The hazard ratios computed for these negative controls will be used to evaluate residual bias and compute calibrated p-values for the outcomes of interest [[1](#_ENREF_1)]. In addition, positive control outcomes (outcomes known to be caused more by the target treatment than the comparator treatment) will be created from negative controls by injecting additional outcomes to the target group. Predictive models of the outcomes will be used to predict baseline probabilities of the outcomes, and these probabilities will be used when injecting new outcomes, injecting the most outcomes for people that were already highest at risk. This is done to ensure that the confounding structure that was present for the negative control is mostly preserved for the positive controls. These positive controls will be used to perform confidence interval calibration.

### Study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the first treatment for depression)

* Exposure to one of the treatments of interest
* At least 365 days of observation time prior to the index date
* No exposure to the two treatments in each pairwise comparison before the index date
* A diagnose of major depressive disorder on or preceding the index date
* No diagnosis of bipolar disorder or schizophrenia on or preceding the index date
* No diagnose of the outcome of interest preceding the index date

### Additional analysis details

The propensity model will be fitted using a regularized logistic regression using L1 regression. The regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation.

The outcome model will be fitted using a Cox regression conditioned on 10 PS strata with only the treatment variable as independent variable.

Positive controls will be generated by using negative controls (where the true relative risk is assumed to be equal to one), and adding additional outcomes to the time at risk of the target cohort. For each negative control outcome, a predictive model will be fitted using L1 regularized survival regression using the same covariates used for the propensity models. The predicted hazard rate for each subject will be used to draw new outcomes. Target true hazard ratios are 1.5, 2, and 4. For more details, see the MethodEvaluation package: <https://github.com/OHDSI/MethodEvaluation>

### Analysis variations

The following variations of the analysis will be performed:

Primary analysis:

* Using a PS model. The outcome model will be condition on the PS strata.

Secondary analysis:

* No PS model, a simple outcome model with only the treatment as predictor.

## Variables

### Exposures

#### All drugs

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient

Inclusion rules based on the index date:

* At least 365 days of observation time prior to the index date
* No exposure to the target or comparator ingredient or procedure before the index date
* A diagnose of major depressive disorder on or preceding the index date
* No diagnose of bipolar disorder or schizophrenia on or preceding the index date
* No diagnose of the outcome of interest preceding the index date

#### Psychotherapy

Initial Event Cohort

People having any of the following: 

* a procedure of mschuemi - Psychotherapy2

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Criteria #1: Prior major depressive disorder

People having all of the following criteria:

* at least 1 occurrences of a condition occurrence of mschuemi - Major depressive disorder1

starting between all days Before and 0 days After event index date

Inclusion Criteria #2: No prior bipolar disorder or schizophrenia

People having all of the following criteria:

* at most 0 occurrences of a condition occurrence of mschuemi - Schizophrenia and bipolar disorder3

starting between all days Before and 0 days After event index date

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. mschuemi - Major depressive disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4152280 | Major depressive disorder | Condition | SNOMED | NO | YES | NO |

2. mschuemi - Psychotherapy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4119335 | Analytical psychology | Procedure | SNOMED | NO | NO | NO |
| 4084202 | Anti-criminal psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4079608 | Anti-suicide psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4048385 | Brief group psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4295027 | Brief solution focused psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4299728 | Client-centered psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4164790 | Conjoint psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4208314 | Couple psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4083706 | Crisis intervention | Procedure | SNOMED | NO | NO | NO |
| 4083131 | Daily life psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4121662 | Developmental psychodynamic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4226276 | Eclectic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4258834 | Educational psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4148765 | Encounter group therapy | Procedure | SNOMED | NO | NO | NO |
| 2007747 | Exploratory verbal psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 4137086 | Expressed emotion family therapy | Procedure | SNOMED | NO | NO | NO |
| 4048387 | Expressive psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4173581 | Extended family therapy | Procedure | SNOMED | NO | NO | NO |
| 46286403 | Family intervention for psychosis | Procedure | SNOMED | NO | NO | NO |
| 2213546 | Family psychotherapy (conjoint psychotherapy) (with patient present) | Procedure | CPT4 | NO | NO | NO |
| 4028920 | Family psychotherapy procedure | Procedure | SNOMED | NO | NO | NO |
| 46286330 | Focal psychodynamic therapy | Procedure | SNOMED | NO | NO | NO |
| 4226275 | Formal psychological therapy | Procedure | SNOMED | NO | NO | NO |
| 45765516 | Functional family therapy | Procedure | SNOMED | NO | NO | NO |
| 4079939 | Functional psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4079500 | General psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4117915 | Generic Jungian-based therapy | Procedure | SNOMED | NO | NO | NO |
| 4100341 | Group analytical psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 44808677 | Group cognitive behavioural therapy | Procedure | SNOMED | NO | NO | NO |
| 4136352 | Group marathon therapy | Procedure | SNOMED | NO | NO | NO |
| 4268909 | Group primal therapy | Procedure | SNOMED | NO | NO | NO |
| 4296166 | Group psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2213548 | Group psychotherapy (other than of a multiple-family group) | Procedure | CPT4 | NO | NO | NO |
| 2617477 | Group psychotherapy other than of a multiple-family group, in a partial hospitalization setting, approximately 45 to 50 minutes | Observation | HCPCS | NO | NO | NO |
| 4196062 | Group reassurance | Procedure | SNOMED | NO | NO | NO |
| 2213554 | Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy); 30 minutes | Procedure | CPT4 | NO | NO | NO |
| 2213555 | Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy); 45 minutes | Procedure | CPT4 | NO | NO | NO |
| 2007730 | Individual psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 4088889 | Individual psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4103512 | Interactive group medical psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2617478 | Interactive group psychotherapy, in a partial hospitalization setting, approximately 45 to 50 minutes | Observation | HCPCS | NO | NO | NO |
| 4221997 | Interactive individual medical psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 40482841 | Interpersonal psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4119334 | Jungian-based therapy | Procedure | SNOMED | NO | NO | NO |
| 4118797 | Long-term exploratory psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4118798 | Long-term psychodynamic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 44792695 | Marital psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2213547 | Multiple-family group psychotherapy | Procedure | CPT4 | NO | NO | NO |
| 4118800 | Narrative family psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4242119 | Occupational social therapy | Observation | SNOMED | NO | NO | NO |
| 2007749 | Other individual psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 2007750 | Other psychotherapy and counselling | Procedure | ICD9Proc | NO | NO | NO |
| 45887728 | Other Psychotherapy Procedures | Procedure | CPT4 | NO | NO | NO |
| 45763911 | Parent-infant psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2007746 | Play psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 4083133 | Potential suicide care | Procedure | SNOMED | NO | NO | NO |
| 4084195 | Provocative therapy | Procedure | SNOMED | NO | NO | NO |
| 2213544 | Psychoanalysis | Procedure | CPT4 | NO | NO | NO |
| 2007731 | Psychoanalysis | Procedure | ICD9Proc | NO | NO | NO |
| 4114491 | Psychoanalytic and psychodynamic therapy | Procedure | SNOMED | NO | NO | NO |
| 2007763 | Psychodrama | Procedure | ICD9Proc | NO | NO | NO |
| 4202234 | Psychodrama | Procedure | SNOMED | NO | NO | NO |
| 4199042 | Psychodynamic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4128268 | Psychodynamic-interpersonal psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4118801 | Psychotherapeutic approaches using specific settings | Procedure | SNOMED | NO | NO | NO |
| 4327941 | Psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4083129 | Psychotherapy - behavioral | Procedure | SNOMED | NO | NO | NO |
| 4079938 | Psychotherapy - cognitive | Procedure | SNOMED | NO | NO | NO |
| 45889353 | Psychotherapy for crisis | Procedure | CPT4 | NO | NO | NO |
| 45888237 | Psychotherapy for Crisis Services and Procedures | Procedure | CPT4 | NO | NO | NO |
| 43527991 | Psychotherapy for crisis; each additional 30 minutes (List separately in addition to code for primary service) | Procedure | CPT4 | NO | NO | NO |
| 43527990 | Psychotherapy for crisis; first 60 minutes | Procedure | CPT4 | NO | NO | NO |
| 45887951 | Psychotherapy Services and Procedures | Procedure | CPT4 | NO | NO | NO |
| 2108571 | Psychotherapy services provided (MDD, MDD ADOL) | Observation | CPT4 | NO | NO | NO |
| 43527986 | Psychotherapy, 30 minutes with patient and/or family member | Procedure | CPT4 | NO | NO | NO |
| 43527987 | Psychotherapy, 30 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure) | Procedure | CPT4 | NO | NO | NO |
| 43527904 | Psychotherapy, 45 minutes with patient and/or family member | Procedure | CPT4 | NO | NO | NO |
| 43527988 | Psychotherapy, 45 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure) | Procedure | CPT4 | NO | NO | NO |
| 43527905 | Psychotherapy, 60 minutes with patient and/or family member | Procedure | CPT4 | NO | NO | NO |
| 43527989 | Psychotherapy, 60 minutes with patient and/or family member when performed with an evaluation and management service (List separately in addition to the code for primary procedure) | Procedure | CPT4 | NO | NO | NO |
| 4148398 | Psychotherapy/sociotherapy | Procedure | SNOMED | NO | NO | NO |
| 4083130 | Rehabilitation for disabling psychiatric problem | Procedure | SNOMED | NO | NO | NO |
| 44791916 | Relationship psychosexual therapy | Procedure | SNOMED | NO | NO | NO |
| 4265313 | Relationship psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4084201 | Samaritans advisory service | Procedure | SNOMED | NO | NO | NO |
| 4233181 | Sensate focus technique | Procedure | SNOMED | NO | NO | NO |
| 4272803 | Sexual psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4035812 | Sexual psychotherapy, female therapist - female patient | Procedure | SNOMED | NO | NO | NO |
| 4012488 | Sexual psychotherapy, female therapist - male patient | Procedure | SNOMED | NO | NO | NO |
| 4132436 | Sexual psychotherapy, group | Procedure | SNOMED | NO | NO | NO |
| 4143316 | Sexual psychotherapy, group, all female | Procedure | SNOMED | NO | NO | NO |
| 4219683 | Sexual psychotherapy, group, all male | Procedure | SNOMED | NO | NO | NO |
| 4151904 | Sexual psychotherapy, group, male and female | Procedure | SNOMED | NO | NO | NO |
| 4278094 | Sexual psychotherapy, male therapist - female patient | Procedure | SNOMED | NO | NO | NO |
| 4249602 | Sexual psychotherapy, male therapist - male patient | Procedure | SNOMED | NO | NO | NO |
| 4234476 | Sexual surrogate therapy | Procedure | SNOMED | NO | NO | NO |
| 4179241 | Short-term psychodynamic therapy | Procedure | SNOMED | NO | NO | NO |
| 4234402 | Social psychotherapy | Observation | SNOMED | NO | NO | NO |
| 4128406 | Specific task orientated psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4080044 | Stimulative psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4262582 | Structural family psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4263758 | Structural psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4126653 | Supportive expressive psychodynamic psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 2007748 | Supportive verbal psychotherapy | Procedure | ICD9Proc | NO | NO | NO |
| 4311943 | Supportive verbal psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4225728 | Suppressive psychotherapy | Procedure | SNOMED | NO | NO | NO |
| 4080048 | Therapeutic psychology | Procedure | SNOMED | NO | NO | NO |
| 44808259 | Therapeutic role play | Procedure | SNOMED | NO | NO | NO |

3. mschuemi - Schizophrenia and bipolar disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 436665 | Bipolar disorder | Condition | SNOMED | NO | YES | NO |
| 435783 | Schizophrenia | Condition | SNOMED | NO | YES | NO |

#### Electroconvulsive therapy

Initial Event Cohort

People having any of the following: 

* a procedure of mschuemi - Electroconvulsive therapy1

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Criteria #1: Prior major depressive disorder

People having all of the following criteria:

* at least 1 occurrences of a condition occurrence of mschuemi - Major depressive disorder2

starting between all days Before and 0 days After event index date

Inclusion Criteria #2: No prior bipolar disorder or schizophrenia

People having all of the following criteria:

* at most 0 occurrences of a condition occurrence of mschuemi - Schizophrenia and bipolar disorder3

starting between all days Before and 0 days After event index date

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. mschuemi - Electroconvulsive therapy

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4111663 | Bilateral electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 4030840 | Electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 2108578 | Electroconvulsive therapy (ECT) provided (MDD) | Observation | CPT4 | NO | NO | NO |
| 2213552 | Electroconvulsive therapy (includes necessary monitoring) | Procedure | CPT4 | NO | NO | NO |
| 4020981 | Electronarcosis | Procedure | SNOMED | NO | NO | NO |
| 4210144 | First treatment in a course of electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 4336318 | Multiple electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 4332436 | Multiple monitored electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |
| 2007728 | Other electroshock therapy | Procedure | ICD9Proc | NO | NO | NO |
| 44508134 | Other specified electroconvulsive therapy | Procedure | OPCS4 | NO | NO | NO |
| 2108579 | Patient referral for electroconvulsive therapy (ECT) documented (MDD) | Observation | CPT4 | NO | NO | NO |
| 2007727 | Subconvulsive electroshock therapy | Procedure | ICD9Proc | NO | NO | NO |
| 4004830 | Subconvulsive electroshock therapy | Procedure | SNOMED | NO | NO | NO |
| 4210145 | Subsequent treatment in a course of electroconvulsive therapy | Procedure | SNOMED | NO | NO | NO |

2. mschuemi - Major depressive disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4152280 | Major depressive disorder | Condition | SNOMED | NO | YES | NO |

3. mschuemi - Schizophrenia and bipolar disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 436665 | Bipolar disorder | Condition | SNOMED | NO | YES | NO |
| 435783 | Schizophrenia | Condition | SNOMED | NO | YES | NO |

### Outcomes

#### Acute liver injury

Initial Event Cohort

People having any of the following: 

* a condition occurrence of acute liver injury1
  + for the first time in the person's history
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

People having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of acute liver injury exclusion concepts2

starting between 365 days Before and 60 days After event index date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. acute liver injury

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 200763 | Chronic hepatitis | Condition | SNOMED | YES | YES | NO |
| 377604 | Hepatic coma | Condition | SNOMED | NO | YES | NO |
| 196029 | Hepatic coma due to viral hepatitis | Condition | SNOMED | YES | YES | NO |
| 4337543 | Hepatic necrosis | Condition | SNOMED | NO | YES | NO |
| 194087 | Hepatitis due to infection | Condition | SNOMED | YES | YES | NO |
| 196455 | Hepatorenal syndrome | Condition | SNOMED | NO | YES | NO |
| 194990 | Inflammatory disease of liver | Condition | SNOMED | NO | YES | NO |
| 4291005 | Viral hepatitis | Condition | SNOMED | YES | YES | NO |

2. acute liver injury exclusion concepts

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 192956 | Cholecystitis | Condition | SNOMED | NO | YES | NO |
| 200763 | Chronic hepatitis | Condition | SNOMED | NO | YES | NO |
| 4212540 | Chronic liver disease | Condition | SNOMED | NO | YES | NO |
| 197917 | Disorder of biliary tract | Condition | SNOMED | NO | YES | NO |
| 192353 | Disorder of gallbladder | Condition | SNOMED | NO | YES | NO |
| 192963 | Disorder of pancreas | Condition | SNOMED | NO | YES | NO |
| 196456 | Gallstone | Condition | SNOMED | NO | YES | NO |
| 4130518 | Neoplasm of liver | Condition | SNOMED | NO | YES | NO |
| 4291005 | Viral hepatitis | Condition | SNOMED | NO | YES | NO |

#### Acute myocardial infarction

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Acute MI1
  + for the first time in the person's history
  + condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Inpatient detail - 1st position, Inpatient header - 1st position
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Acute MI

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |

#### Alopecia

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Alopecia1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Alopecia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 133280 | Alopecia | Condition | SNOMED | NO | YES | NO |
| 133959 | Syphilitic alopecia | Condition | SNOMED | YES | YES | NO |

#### Constipation

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Constipation1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Constipation

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 75860 | Constipation | Condition | SNOMED | NO | YES | NO |

#### Decreased libido

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Decreased libido1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Decreased libido

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 436246 | Reduced libido | Condition | SNOMED | NO | YES | NO |

#### Delirium

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Delirium1
  + for the first time in the person's history
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Delirium

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 377830 | Alcohol withdrawal delirium | Condition | SNOMED | YES | YES | NO |
| 373995 | Delirium | Condition | SNOMED | NO | YES | NO |

#### Diarrhea

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Diarrhea1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Diarrhea

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 196523 | Diarrhea | Condition | SNOMED | NO | YES | NO |
| 80141 | Functional diarrhea | Condition | SNOMED | NO | YES | NO |

#### Fracture

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Fracture1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Fracture

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 435093 | Closed fracture of femur | Condition | SNOMED | NO | YES | NO |
| 441974 | Closed fracture of forearm | Condition | SNOMED | NO | YES | NO |
| 4230399 | Closed fracture of hip | Condition | SNOMED | NO | YES | NO |
| 441422 | Closed fracture of humerus | Condition | SNOMED | NO | YES | NO |
| 439166 | Closed fracture of radius | Condition | SNOMED | NO | YES | NO |
| 4278672 | Fracture of forearm | Condition | SNOMED | NO | YES | NO |
| 442619 | Fracture of humerus | Condition | SNOMED | NO | YES | NO |
| 433856 | Fracture of neck of femur | Condition | SNOMED | NO | YES | NO |
| 4131595 | Fracture of radius | Condition | SNOMED | NO | YES | NO |
| 73571 | Pathological fracture | Condition | SNOMED | NO | YES | NO |

#### Gastrointestinal hemhorrage

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Gastrointestinal hemorrhage1
  + for the first time in the person's history
  + condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Inpatient detail - 1st position, Inpatient header - 1st position
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Gastrointestinal hemorrhage

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4280942 | Acute gastrojejunal ulcer with perforation | Condition | SNOMED | NO | YES | NO |
| 28779 | Bleeding esophageal varices | Condition | SNOMED | NO | YES | NO |
| 198798 | Dieulafoy's vascular malformation | Condition | SNOMED | NO | YES | NO |
| 4112183 | Esophageal varices with bleeding, associated with another disorder | Condition | SNOMED | NO | YES | NO |
| 194382 | External hemorrhoids | Condition | SNOMED | NO | NO | NO |
| 192671 | Gastrointestinal hemorrhage | Condition | SNOMED | NO | YES | NO |
| 196436 | Internal hemorrhoids | Condition | SNOMED | NO | NO | NO |
| 4338225 | Peptic ulcer with perforation | Condition | SNOMED | NO | YES | NO |
| 194158 | Perinatal gastrointestinal hemorrhage | Condition | SNOMED | YES | YES | NO |

#### Hyperprolactinemia

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hyperprolactinemia1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Hyperprolactinemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4030186 | Hyperprolactinemia | Condition | SNOMED | NO | YES | NO |

#### Hyponatremia

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hyponatremia1
  + for the first time in the person's history
* a measurement of Serum sodium2
  + for the first time in the person's history
  + with value as number < 136
  + unit is any of: millimole per liter

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Hyponatremia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 435515 | Hypo-osmolality and or hyponatremia | Condition | SNOMED | NO | YES | NO |

2. Serum sodium

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 3032987 | Sodium [Moles/volume] corrected for glucose in Serum or Plasma | Measurement | LOINC | NO | YES | NO |
| 46235784 | Sodium [Moles/volume] in Serum, Plasma or Blood | Measurement | LOINC | NO | YES | NO |
| 3019550 | Sodium serum/plasma | Measurement | LOINC | NO | YES | NO |

#### Hypotension

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hypotension1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Hypotension

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4120275 | Drug-induced hypotension | Condition | SNOMED | NO | YES | NO |
| 317002 | Low blood pressure | Condition | SNOMED | NO | YES | NO |
| 314432 | Maternal hypotension syndrome | Condition | SNOMED | YES | YES | NO |
| 319041 | Orthostatic hypotension | Condition | SNOMED | NO | YES | NO |

#### Hypothyroidism

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Hypothyroidism1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

People having all of the following criteria:

* at least 2 occurrences of a condition occurrence of Hypothyroidism1

starting between 0 days Before and 90 days After event index date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Hypothyroidism

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 140673 | Hypothyroidism | Condition | SNOMED | NO | YES | NO |

#### Insomnia

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Insomnia1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Insomnia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 439708 | Disorders of initiating and maintaining sleep | Condition | SNOMED | NO | YES | NO |
| 436962 | Insomnia | Condition | SNOMED | NO | YES | NO |
| 4305303 | Sleep deprivation | Condition | SNOMED | NO | YES | NO |

#### Nausea

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Nausea1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Nausea

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 30284 | Motion sickness | Condition | SNOMED | YES | YES | NO |
| 31967 | Nausea | Condition | SNOMED | NO | YES | NO |

#### Open-angle glaucoma

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Open-angle glaucoma1
  + for the first time in the person's history

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

For people matching the Primary Events, include:

People having all of the following criteria:

* at least 1 occurrences of a condition occurrence of Open-angle glaucoma1
  + provider specialty is any of: Ophthalmology, Optometry, Optician

starting between 1 days After and 365 days After event index date

Limit cohort of initial events to: **earliest event per person.**

Limit qualifying cohort to: **all events per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Open-angle glaucoma

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 432908 | Glaucomatocyclitic crisis | Condition | SNOMED | YES | YES | NO |
| 441561 | Low tension glaucoma | Condition | SNOMED | NO | YES | NO |
| 4216823 | Open angle with borderline findings | Condition | SNOMED | YES | YES | NO |
| 441284 | Open-angle glaucoma | Condition | SNOMED | NO | YES | NO |
| 4072218 | Secondary open-angle glaucoma | Condition | SNOMED | YES | YES | NO |

#### Seizure

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Seizure and seizure disorder1
  + for the first time in the person's history
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Seizure and seizure disorder

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 380533 | Convulsions in the newborn | Condition | SNOMED | YES | YES | NO |
| 45757050 | Epilepsy in mother complicating pregnancy | Condition | SNOMED | YES | YES | NO |
| 377091 | Seizure | Condition | SNOMED | NO | YES | NO |
| 4029498 | Seizure disorder | Condition | SNOMED | NO | YES | NO |

#### Stroke

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Ischemic stroke1
  + for the first time in the person's history
  + visit occurrence is any of: Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Ischemic stroke

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 374060 | Acute ill-defined cerebrovascular disease | Condition | SNOMED | NO | YES | NO |
| 4108356 | Cerebral infarction due to embolism of cerebral arteries | Condition | SNOMED | NO | YES | NO |
| 4110192 | Cerebral infarction due to thrombosis of cerebral arteries | Condition | SNOMED | NO | YES | NO |
| 4043731 | Infarction - precerebral | Condition | SNOMED | NO | YES | NO |

#### Suicide and suicidal ideation

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Suicide and suicidal ideation1
  + for the first time in the person's history
* an observation of Suicide and suicidal ideation1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Suicide and suicidal ideation

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 439235 | Self inflicted injury | Condition | SNOMED | NO | YES | NO |
| 4181216 | Self-administered poisoning | Condition | SNOMED | NO | YES | NO |
| 444362 | Suicidal deliberate poisoning | Condition | SNOMED | NO | YES | NO |
| 4273391 | Suicidal thoughts | Condition | SNOMED | NO | YES | NO |
| 440925 | Suicide | Observation | SNOMED | NO | YES | NO |

#### Tinnitus

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Tinnitus1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Tinnitus

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 377575 | Tinnitus | Condition | SNOMED | NO | YES | NO |

#### Ventricular arrhythmia and sudden cardiac death

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Ventricular arrhythmia and sudden cardiac death1
  + for the first time in the person's history
  + condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Carrier claim detail - 1st position, Carrier claim header - 1st position, Inpatient detail - 1st position, Inpatient header - 1st position, Outpatient detail - 1st position, Outpatient header - 1st position
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Ventricular arrhythmia and sudden cardiac death

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 321042 | Cardiac arrest | Condition | SNOMED | NO | YES | NO |
| 442289 | Death in less than 24 hours from onset of symptoms | Observation | SNOMED | NO | YES | NO |
| 441139 | Instantaneous death | Observation | SNOMED | NO | YES | NO |
| 4132309 | Sudden death | Observation | SNOMED | NO | YES | NO |
| 4185572 | Ventricular arrhythmia | Condition | SNOMED | NO | YES | NO |
| 437894 | Ventricular fibrillation | Condition | SNOMED | NO | YES | NO |
| 4103295 | Ventricular tachycardia | Condition | SNOMED | NO | YES | NO |

#### Vertigo

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Vertigo1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Vertigo

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 78162 | Peripheral vertigo | Condition | SNOMED | NO | YES | NO |
| 439383 | Vertigo | Condition | SNOMED | NO | YES | NO |
| 381035 | Vertigo of central origin | Condition | SNOMED | NO | YES | NO |

### Potential confounders

The following will be included as potential covariates: (note: most covariates are assessed on or in the 365 days prior to index date)

* Demographics (age in 5-year increments, gender, race, ethnicity, year of index date, month of index date)
* Condition occurrence (one or more variables per diagnose code)
* Condition era (one or more variables per diagnose code)
* Condition group (one or more variables per MedDRA group or SNOMED groups)
* Drug exposure (one or more variables per drug code)
* Drug era (one or more variables per RxNorm ingredient)
* Drug group (one or more variables per ATC group)
* Procedure occurrence (one or more variables per procedure code)
* Observations (one or more variables per observation concept ID)
* Measurements (one or more variables per measurement concept ID, including variables for within / above / below normal range)
* Risk scores (including Charleston, DCSI, CHADS2, CHADS2VASc

For the full details see the OHDSI CohortMethod package (<https://github.com/OHDSI/CohortMethod>).

Variables with less than 100 non-zero values are discarded.

### Negative controls

Negative controls were defined as any of the following diagnoses:

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  | | --- | --- | | Acariasis | Ingrowing nail | | Amyloidosis | Iridocyclitis | | Ankylosing spondylitis | Irritable bowel syndrome | | Aseptic necrosis of bone | Lesion of cervix | | Astigmatism | Lyme disease | | Bell's palsy | Malignant neoplasm of endocrine gland | | Benign epithelial neoplasm of skin | Mononeuropathy | | Chalazion | Onychomycosis | | Chondromalacia | Osteochondropathy | | Crohn's disease | Paraplegia | | Croup | Polyp of intestine | | Diabetic oculopathy | Presbyopia | | Endocarditis | Pulmonary tuberculosis | | Endometrial hyperplasia | Rectal mass | | Enthesopathy | Sarcoidosis | | Epicondylitis | Scar | | Epstein-Barr virus disease | Seborrheic keratosis | | Fracture of upper limb | Septic shock | | Gallstone | Sjogren's syndrome | | Genital herpes simplex | Tietze's disease | | Hemangioma | Tonsillitis | | Hodgkin's disease | Toxic goiter | | Human papilloma virus infection | Ulcerative colitis | | Hypoglycemic coma | Viral conjunctivitis | | Hypopituitarism | Viral hepatitis | | Impetigo | Visceroptosis | |  |  |
|  |  |  |

### Other variables

Major depressive disorder will be identified using the concept for major depressive disorder and any of its descendants in the OMOP Vocabulary.

Bipolar disorder will be identified using the concept for bipolar disorder and any of its descendants in the OMOP Vocabulary.

Schizophrenia will be identified using the concept for schizophrenia and any of its descendants in the OMOP Vocabulary.

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 4 or OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 4 is available at: <http://omop.org/cdm>. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>. The following databases will be included in this analysis:

* Truven MarketScan Commercial Claims and Encounters (CCAE)
* Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)
* Truven MarketScan Multi-state Medicaid (MDCD)
* Optum ClinFormatics (Optum)
* <<add others who agree to participate>>

Truven MarketScan Commercial Claims and Encounters (CCAE)

CCAE is an administrative health claims database for active employees, early retirees, COBRA continues, and their dependents insured by employer-sponsored plans (individuals in plans or product lines with fee-for-service plans and fully capitated or partially capitated plans). As of 30November2014, CCAE contained 117m patients with patient-level observations from Jan2000 through Jul2014. Source codes used in CCAE include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming CCAE into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_ccae/dashboard>.

Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)

MDCR is an administrative health claims database for Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans (predominantly fee-for-service plans). Only plans where both the Medicare-paid amounts and the employer-paid amounts were available and evident on the claims were selected for this database.. As of 30November2014, MDCR contained 9m patients with patient-level observations from Jan2000 through Jul2014. Source codes used in MDCR include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming MDCR into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_mdcr/dashboard>.

Truven MarketScan Multi-state Medicaid (MDCD)

MDCD is an administrative health claims database for the pooled healthcare experience of Medicaid enrollees from multiple states. As of 30November2014, MDCD contained 16m patients with patient-level observations from Jan2006 through Dec2012. Source codes used in MDCD include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming MDCD into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_mdcd/dashboard>.

Optum ClinFormatics (Optum)

Optum is an administrative health claims database for members of United Healthcare, who enrolled in commercial plans (including ASO, 36.31M), Medicaid (prior to July 2010, 1.25M) and Legacy Medicare Choice (prior to January 2006, 0.36M) with both medical and prescription drug coverage. As of 30November2014, Optum contained 38m patients with patient-level observations from Oct2005 through Dec2013. Source codes used in Optum include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming Optum into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/optum/dashboard>.

*Database X*

*Database X description*

The ETL specification for transforming *Database X* into the OMOP CDM is available at:  *ETL\_specification\_URL*

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available at: *URL to ACHILLES*.

## Sample Size and Study Power

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## Quality control

We will evaluate the PS by

* Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
* Inspection of the PS distribution.
* Evaluation of covariate balance after stratification using the standardized difference in means between treatment and comparator cohort before and after matching [[2](#_ENREF_2)]. Standardized differences greater than 0.2 will be reported and investigated.

The error distribution estimated using the negative and positive controls will be used to estimate residual bias after adjustments.

The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation.

## Strengths and Limitations of the Research Methods

Strength

* Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS stratification allows balancing on a large number of baseline potential confounders.
* Use of negative and positive control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.
* It is unknown whether and to what extends misclassification of any of the outcomes occurs, and whether any such misclassification affects the results. Because we are using outcome controls, we cannot use these to measure bias that is specific to the outcomes of interest.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

# References

1. Schuemie MJ, Ryan PB, DuMouchel W, et al. Interpreting observational studies: why empirical calibration is needed to correct p-values. Statistics in medicine 2014;**33**(2):209-18 doi: 10.1002/sim.5925[published Online First: Epub Date]|.

2. Austin PC. Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. Pharmacoepidemiology and drug safety 2008;**17**(12):1218-25 doi: 10.1002/pds.1674[published Online First: Epub Date]|.